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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,649	10/05/2001	Monica Jonsson	003300-833	2032

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EXAMINER	
HUI, SAN MING R	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 06/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,649	JONSSON ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42,44 and 46-84* is/are pending in the application.

4a) Of the above claim(s) *38-42, 44, 46-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37 and 60-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 17, 2004 has been entered.

Claims 1-42, 44, 46-84 are pending. Claims 38-42, 44, 46-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The outstanding rejection under 35 USC 112, second paragraph with regard to "highly viscous solution " has been withdrawn in view of the amendments filed February 17, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "reversibly solidified active substance" in claim 4 renders the claims indefinite as to what substance are encompassed by the claims.

Response to arguments

Applicant's rebuttal arguments filed February 17, 2004 averring the term "reversibly solidified" being defined in the specification have been considered, but are found persuasive. It is not the term "reversibly solidified" unclear in view of the instant specification. It is the term "reversibly solidified active substance" renders the claim indefinite because it is not clear what compounds or active substances are considered "reversibly solidified". The metes and bounds of the claims cannot be ascertained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-37 and 60-84 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,616,949 ('949). Although the conflicting claims are not

identical, they are not patentably distinct from each other because '949 teaches an almost exactly the same method of preparing microparticles. '949 teaches the instant method steps a)-h) with the different wordings of step b) reciting that the solution of step a) be concentrated with solution of polyethylene glycol. '949 teaches the PEG employed can be with molecular weight 400-100,000kDa.

'949 does not expressly teach the instant concentration of PEG. '949 does not expressly teach the herein molecular weight of PEG. '949 does not expressly teach temperature of the mixing condition.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed concentration and molecular weight of PEG into the method of '949. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the instant composition in the temperature as recited.

One of ordinary skill in the art would have been motivated to employ the herein claimed concentration and molecular weight of PEG into the method of '949. The optimization of result effect parameters (e.g., the concentration and molecular weight of PEG) is obvious as being within the skill of the artisan. Furthermore, one of ordinary skill in the art would have been motivated to prepare the instant composition in the temperature as recited since optimization of the result effect parameters, such as mixing conditions, would be within the purview of skilled artisan.

Claims 1-37 and 60-84 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,706,288 ('288). Although the conflicting claims are not identical, they are not patentably distinct from each other because '288 teaches an almost exactly the same method of preparing microparticles with different order. '288 teaches the instant method steps of making the starch solution or suspension first and then combine with the solution of active substance. Afterwards, combining the resulting composition with PEG solution. '288 teaches the PEG employed can be with molecular weight 100-4,000kDa, and most prefer 300-600kDa. '288 teaches the combination steps were carried in temperature of 30-37°C.

'288 does not expressly teach the specific order of mixing the ingredients together.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the specific order of mixing the ingredients together.

One of ordinary skill in the art would have been motivated to employ specific order of mixing the ingredients together. Absent evidence to the contrary, simply mixing together the same ingredients in a different order would be obvious to one of ordinary skill in the art because adding A to B and mix would be considered the same as adding B to A and mix.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-37 and 60-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woiszwillo et al. (US Patent 5,981,719 from IDS received January 22, 2002), Ekman et al. (US Patent 4,822,535) in view of Laakso et al.

(Journal of Pharmaceutical Sciences, 1986;75(10):962-967 from IDS received January 22, 2002) and Takada et al. (US Patent 5,622,657 from IDS received January 22, 2002), references of record in previous office action mailed February 26, 2003.

Woiszwillo et al. teaches a method of preparing biological active microparticles suitable for parenteral administration by mixing an aqueous solution of bioactive compounds, such as insulin, leuprolide, and bovine Serum Albumin, with the solution of polyethylene glycol. The microparticles are collected after heating to temperature between 37 - 70°C, centrifuging and washing (See col. 21, line 11-34; also col. 5, line 65 - col.7, line 49). Woiszwillo et al. also teaches the biological active substances as enzymes, recombinant proteins, polypeptide, carbonhydrate, such as insulin, leuprolide, and Bovine Serum Albumin (See col. 7, line 50 – col. 8, line 32). Woiszwillo et al. also teaches the concentration of the polymer as between 5-50% (see col. 11, line 48). Woiszwillo et al. also teaches the solution of preferred polymers, including polyethylene glycol, having molecular weight of 3,000 to 500,000 daltons can be added to the solution of the macromolecules in order to form a microparticles (See col. 12, lines 33-42). Woiszwillo et al. also teaches the way to optimizing the microparticles by altering the particle size and temperature (See col. 13, lines 30-36).

Ekman et al. teaches a method to encapsulate bioactive substance in order to form a solid microparticles by employing a two-phase emulsion system (See abstract, also col. 9, line 13 – 26). Ekman et al. teaches the two-phase

system suitable for the preparation of such microparticle as polyethylene glycol/soluble starch/water (See col. 2, line 11-12). Ekman et al. also teaches the drying steps may be accomplished by evaporation or ultrafiltration, in which evaporation would include heating or reduced pressure (e.g., freeze-drying) (See col. 3, line 1-8). Ekman et al. also teaches the polyethylene glycol as preferred polymer and its molecular weight as 100-2,000,000 Da (See col. 4, line 36).

The references do not expressly teach the method of preparing microparticles by employing the method of Woiszwillo et al. followed by that of Ekman et al. The references do not expressly teach the herein claimed characteristics (i.e., nitrogen content, particle size, and amyloprectin content) of starch employed. The references do not expressly teach the optional steps recited in claims 35-37. The references do not expressly teach the herein claimed temperature employed. The references do not expressly teach the herein claimed concentrations and molecular weight of polyethylene glycol.

Laakso et al. teaches polyacryl starch is suitable as carrier for passive target drug delivery since polyacryl starch is rapidly taken up by the reticuloendothelial system (RES) (see the abstract). Laakso et al. also teaches the nitrogen content of polyacryl starch can be affected by the amount of initiator employed (See the abstract and figure 2 in page 964). Laakso et al. teaches the degradation of polyacryl starch can be affected by the amount of initiator employed and the degree of derivatization of the starch (See particularly the abstract and page 966-967, Discussion Section).

Takada et al. teaches a prolonged release biological active microparticles which is coated by copolymers of poyllactic/glycolic acid (See col. 7, line 15-53). Takada et al. teaches such sustained release formulation is useful for various peptides and hormones (See col. 3, line 28 – col. 4, line 34).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the herein claimed microparticles by employing the method of preparing microparticles by employing the method of Woiszwillo et al. followed by that of Ekman et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the suitable starch compounds herein claimed in the method of preparing the herein claimed microparticles. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed temperature and particle size in the herein claimed method. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed materials for preparing the optional sustained release shell for the microparticle. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed temperature as well as concentrations and molecular weight of polyethylene glycol in preparing the herein claimed microparticles.

One of ordinary skill in the art would have been motivated to prepare the herein claimed microparticles by employing the method of Woiszwillo et al. followed by that of Ekman et al. because Woiszwillo et al.'s method is to prepare

a microparticle and then Ekman et al. would further encapsulate such microparticle to increasing the stability of the biological active substances.

One of ordinary skill in the art would have been motivated to employ the suitable starch compounds herein claimed in the method of preparing the herein claimed microparticles since the polyacryl starch is well-known as useful for passive targeting drug delivery. Optimizing the nitrogen content, molecular weight, the starch solution concentration, the weight ratio between the biological active substance and starch, the temperature employed, and particle size would be considered obvious as being within the purview of skilled artisan.

One of ordinary skill in the art would have been motivated to employ the herein claimed materials for preparing the optional sustained release shell for the microparticle since such materials are well-known to be useful as sustained release material for peptide medicine. Employing the herein claimed polymer as sustained release shell would have been reasonably expected to be similarly useful.

One of ordinary skill in the art would have been motivated to employ the herein claimed temperature as well as concentrations and molecular weight of polyethylene glycol in preparing the herein claimed microparticles. Optimization is seen to be within the purview of the skilled artisan, absent evidence to the contrary.

Response to Arguments

Applicant's arguments filed February 17, 2004 averring Ekman not capable modifying the teachings of Woiszwillo in arriving the instant invention have been fully considered but they are not persuasive. Applicants' argues that Woiszwillo teaches a method of preparing micropaticle with single phase whereas Ekman teaches a method of preparing micropaticle with a two-phase system not being compatible. A two-phase or multi-pahse system is always involving in two or more immiscible systems. Using Woiszwillo's sytem as one of the immiscible system and apply it to Ekman's system would seems to be reasonable and obvious. Moreover, the benefit of employing the method of Woiszwillo followed by that of Ekman would be the stability increase of the biological active substances. The microparticles prepared by Woiszwillo et al.'s method can be further encapsulated by Ekman et al.'s method. That is from a single phrase process moving to a two-phase process just as herein recited.

Applicant's arguments filed February 17, 2004 averring no motivation being provided by the cited prior art have been considered, but are not found persuasive. As discussed above, the motivation to modify the method of Ekman and Woiszwillo is that it will provide a microparticles that is further stabilized by Ekman's method.

Applicant's arguments filed February 17, 2004 averring no reasonable expectation of success was provided by the cited prior art have been considered, but are not found persuasive. There is no reason provided by the applicant pointing that no reasonable expectation of success other than the point that Ekman and Woiszwillo are using two-phase system and single phase system

respectively. As discussed above, there is no reason why Woiszwillo's system cannot be used as one of the two-phase system taught in Ekman.

Applicant's arguments filed February 17, 2004 averring there being no need to further modify Woiszwillo's microparticle because they are ready to use have been considered but are not found persuasive. The motivation to combine the teachings of Ekman and Woiszwillo is to further stabilize the microparticles containing biological active substances. It is not clear why further stabilization of biological active substances as enzymes, recombinant proteins, polypeptide, carbonhydrate, such as insulin, leuprolide, and Bovine Serum Albumin would be "counterintuitive" and "backwards" to one skilled in the art. Applicant has not provided sufficient evidence to rebut the Examiner's position other than simply alleging the motivation not being provided.

Applicant's arguments filed February 17, 2004 averring one skilled in the art would recognize that the teachings of Ekman and Woiszwillo are not realistically combinable have been considered, but are not found persuasive. It is unclear why the teachings of Ekman and Woiszwillo are not combinable. As discussed above, the single phase systems produced by Woiszwillo can be used as one of the phases in the two-phase system in Ekman.

The only reason for incompatibility of Ekman and Woiszwillo cited by the applicant in the response filed February 17, 2004 is that Ekman employs a two-phase system and Woiszwillo employs a single phase. In view of the discussion above, Examiner does not consider such reason as sufficient to obviate the

outstanding rejection under 35 USC 103(a). Therefore, the claims are still considered as rejected properly under 35 USC 103(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Patent Examiner
Art Unit 1617